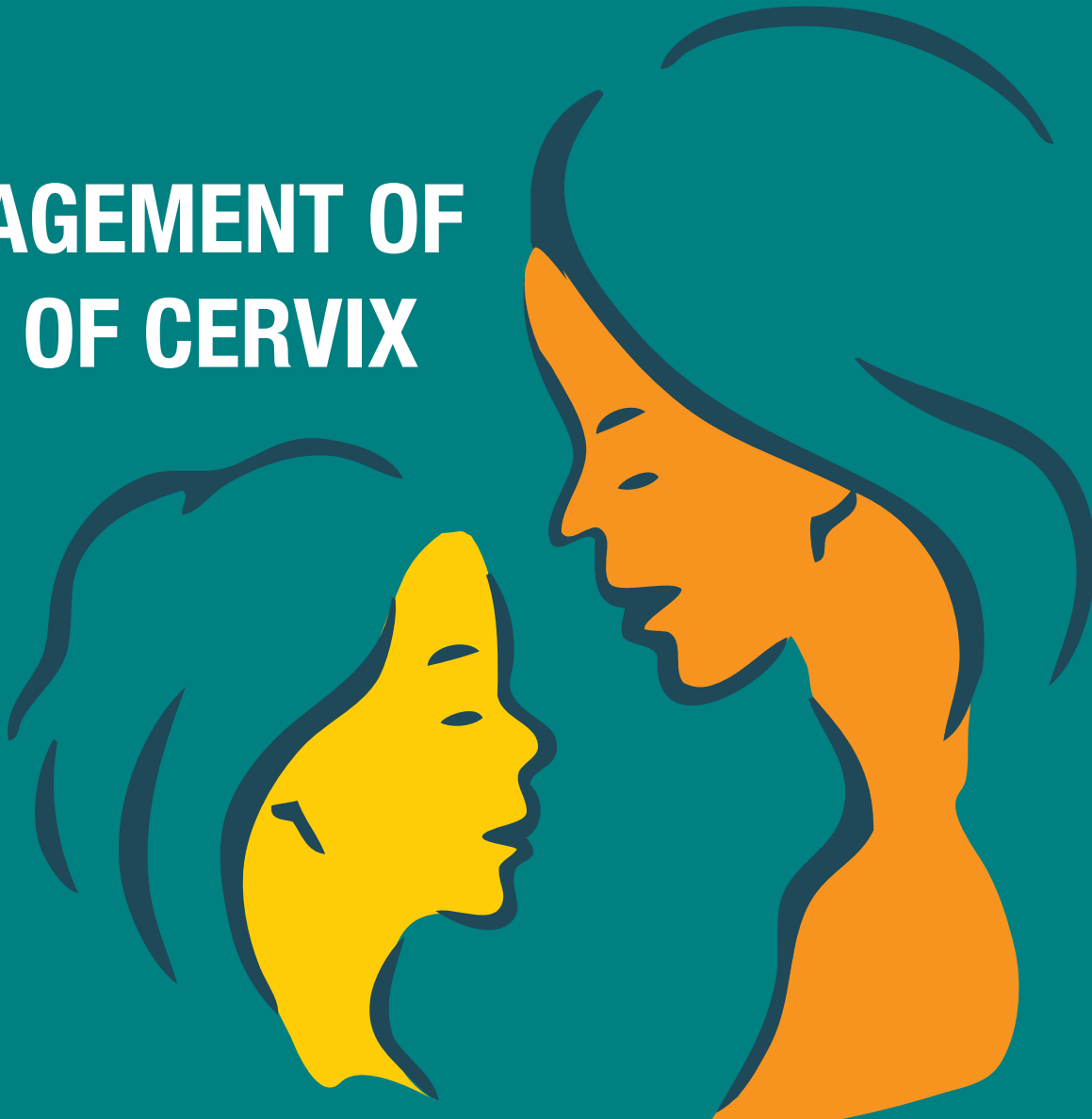
FOGSI GCPR

SCREENING AND MANAGEMENT OF PREINVASIVE LESIONS OF CERVIX AND HPV VACCINATION



FOGSI GYNAECOLOGIC ONCOLOGY COMMITTEE

January, 2018

Introduction

DR NEERJA BHATLA
Chairperson
FOGSI Gynaecologic Oncology Committee

India is a land of diversity and this is reflected also in the varied practices followed for cervical screening. For years we have followed guidelines of various foreign societies, simultaneously lamenting the lack of uniformity of resources in our country. Also, each one of us works across different scenarios, sometimes in a tertiary hospital with state of the art facilities and sometimes in an outreach clinic or camp setting. The FOGSI Gynaecologic Oncology Committee takes great pleasure in presenting Good Clinical Practice Recommendations (GCPR) for cervical cancer prevention in the Indian context. The first step is to identify which situation you are working in – good resource or low resource – and accordingly to identify the options for screening, triage for confirmation of diagnosis and management.

Recognising that the bulk of cervical cancer in India manifests after the age of 30 years, FOGSI recommends that screening should be started at 25 years for good resource and 30 years for low resource settings. FOGSI recognises that while HPV testing is the best method, all the screening tests, namely, HPV, cytology, co-testing with both HPV and cytology, and VIA, are all valid options. The critical steps are maintenance of quality control as well as follow-up and treatment of screen detected lesions. Single visit approach is to be practiced wherever possible to minimise non-compliance and loss to follow-up. The charts show the screening algorithms for each type of screening method and management of various grades of CIN. All options have been evaluated and recommended based on global evidence and international guidelines, resource based recommendations, e.g., WHO and ASCO, and Indian data and recommendations of the Ministry of Health & Family Welfare. These have been extensively reviewed by the group of experts and summarized in the GCPR. Acceptable options have been offered wherever it was felt necessary based on expert opinion.

Primary prevention with HPV vaccine is strongly recommended. FOGSI endorses the WHO recommendation that the preferred age group is under 15 years, where two doses can be administered at an interval of 6 months. The charts also outline the recommendations for older girls and women as well as for special situations. It is to be emphasised that screening must continue after vaccination too.

This work would not have been possible without the inspiration from our seniors and the hard work and commitment of the expert panel. I am grateful to each one of them for their untiring support and contributions. I am also thankful to PSI for their partnership and support to bring this work to fruition. The detailed document with references and explanations of levels of evidence can be accessed online at www.fogsi.org. I am confident that you will find the FOGSI GCPR useful in your day-to-day practice and helpful in our common battle to eliminate cervical cancer.

January 17, 2018

FOGSI Good Clinical Practice Recommendation

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HPV VACCINATION

FOGSI GCPR: HPV Vaccination

	FOGSI RECOMMENDATION	STRENGTH OF RECOMMENDATION
Types of vaccines	Bivalent (Cervarix, GSK) Quadrivalent (Gardasil, Merck)	NA
License to use in India	9 - 45 years	NA
Preferred target age group	9 - 14 years	Grade A
Number of doses for girls aged < 15 years, not immunocompromised or HIV infected	2 doses	Grade A
Number of doses for girls aged ≥ 15 years or immunocompromised and/or HIV infected girls	3 doses	Grade A

FOGSI GCPR: HPV Vaccination

	FOGSI RECOMMENDATION	STRENGTH OF RECOMMENDATION
Interval	**Two doses:** 0 & 6 months (second dose may be given at 5-15 months) **Three doses:** 0, 1, 6 months (Bivalent) 0, 2, 6 months (Quadrivalent)	Grade A
Catch-up vaccination (15-26 years)	• 3 doses • Girls/ women who have been sexually active should be counselled regarding **reduced efficacy** and **importance of screening** from the age of 25-30 years (Not to be considered in public programs unless resources are available after vaccinating and screening the respective target age groups)	Grade B
Older age groups (> 26 years)	• 3 doses • Women aged > 26 years who have been sexually active should be counselled regarding **reduced efficacy** in older age group and the **importance of screening** • In limited-resource settings, women in this age group should first invest in screening	Grade B

FOGSI GCPR: HPV Vaccination (Special Situations)

	FOGSI RECOMMENDATION	STRENGTH OF RECOMMENDATION
HIV positive or immunocompromised girls	• Same age recommendation • Three doses	Grade A
Interrupted doses	• Continue with the remaining doses as per age-based recommendation, vaccination series need not be restarted	Grade B
Pregnancy and Lactation	• Not recommended in pregnancy (if inadvertently given, no need for MTP) • Can be given during lactation	Grade B
Victims of sexual abuse	• Same age recommendation • Three doses • Initiate preferably at the time of examination at health care facility	Grade B
Women with history of abnormal screening reports	• Same age recommendation • Women should be counselled regarding **reduced efficacy** in older age group and the **importance of regular follow-up**	Grade B

SCREENING AND TREATMENT OF PREINVASIVE LESIONS OF CERVIX

Criteria of Various Single Visit Approach Strategies

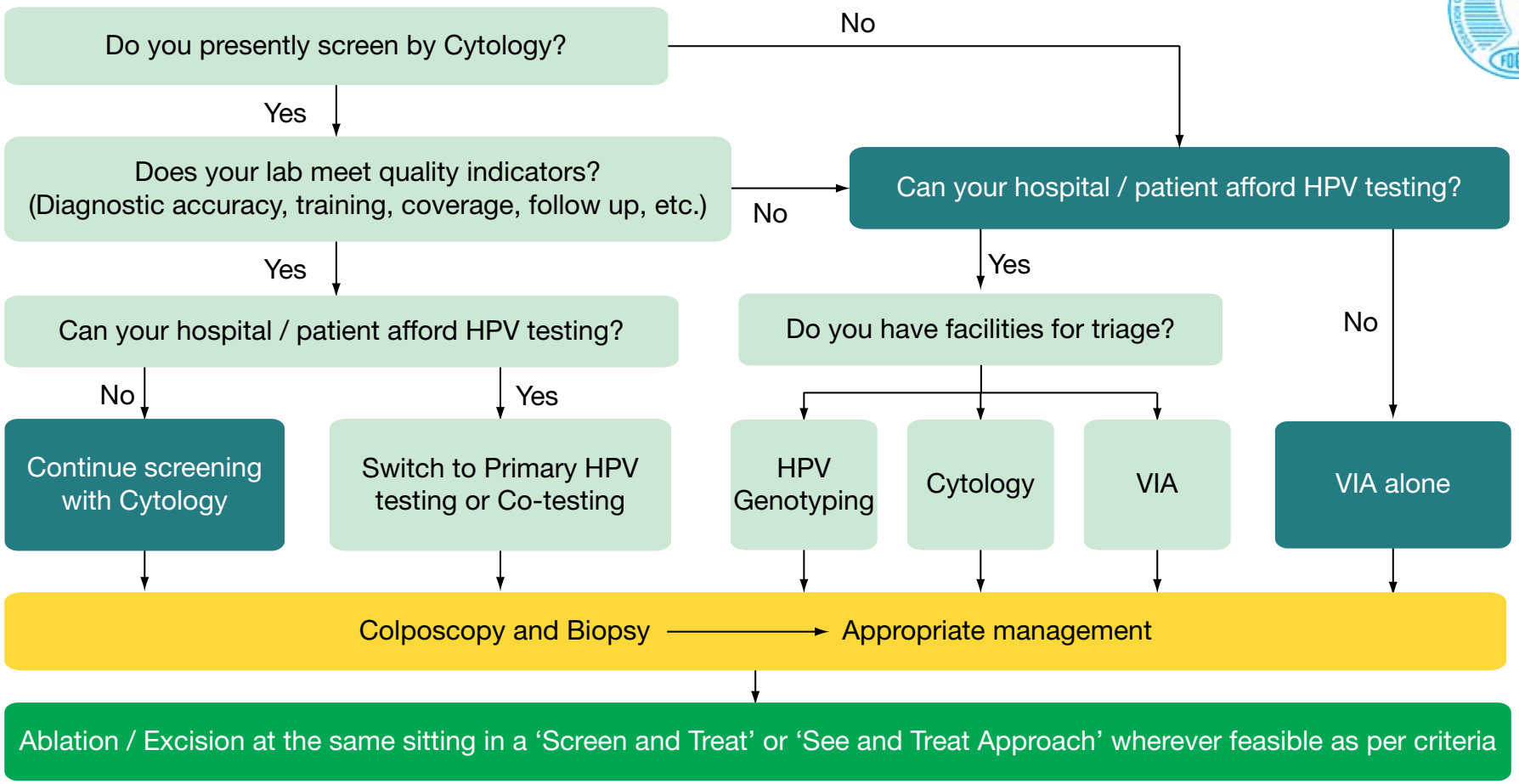
See and Treat

- In Colposcopy Clinics
- Patient referred with abnormal cytology report
- Colposcopy scoring indicates a high grade lesion
- Simultaneous treatment done – excision or ablation
- Low probability of over-treatment because of high specificity of cytology
- Post-hoc analysis of biopsy report/excision specimen

Screen and Treat

- In Public Health Programs
- VIA detects abnormal lesion
- Criteria for ablation fulfilled
- Treat immediately, with or without biopsy
- Lower probability of over-treatment in high prevalence areas
- Post-hoc analysis is possible if biopsy taken

Choosing the Most Appropriate Screening Test for Your Practice



Adapted from WHO Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention.

Resource-Based Strategies for Cervical Cancer Screening and Management of CIN

SETTING	SCREENING TOOLS	TRIAGE TOOLS	MANAGEMENT OPTIONS	SINGLE VISIT APPROACH
Good resource settings	Primary HPV test *or* Co-testing (HPV test + Cytology) *or* Cytology *or* VIA	Cytology ± newer modalities* HPV test HPV Genotyping-16/18 Colposcopy and biopsy** VIA and biopsy**	LEEP Conization Cryotherapy Thermal coagulation	See and Treat approach
Limited resource settings#	VIA HPV#	Colposcopy, if available Biopsy**	Cryotherapy LEEP Conization Thermal coagulation	Screen and Treat *or* Screen, See and Treat approach

* Newer modalities (p16, Ki 67 testing, mRNA testing, E6,E7 protein testing).

** Biopsy from any abnormal area(s)

Affordable HPV test (if available), including self-sampling, can be used.

Resource-based Cervical Cancer Screening Recommendation

	GOOD RESOURCE SETTINGS	LIMITED RESOURCE SETTINGS
Modalities	HPV testing • Primary HPV testing • Co-testing (HPV & cytology) Cytology VIA	VIA (Affordable HPV testing may be introduced if feasible)
Target Age Group (years)	25 - 65	30 - 65 (N.B.: In postmenopausal women, screening with VIA may not be as effective)
Age to start (years)	Cytology at 25 Primary HPV Testing / Co-testing at 30	VIA at 30
Frequency	Primary HPV Testing *or* Co-testing – every 5 years Cytology – every 3 years	Every 5 years (at least 1-3 times in a lifetime)

Resource-based Cervical Cancer Screening Recommendation

	GOOD RESOURCE SETTINGS	LIMITED RESOURCE SETTINGS
Age to stop (years)	• 65 with consistent negative results in last 15 years • Women with no prior screening should undergo tests once at 65 years and, if negative, they should exit screening.	
Follow-up method after treatment; interval	HPV testing (preferred) *or* cytology 12 months	VIA 12 months
Screening following abnormal reports ≥ CIN 2+, irrespective of method of treatment	20 years	
Screening in hysterectomized women	• Following hysterectomy in which cervix was removed for benign causes : no need for screening, unless there is history of previous cervical intraepithelial neoplasia (CIN) • Absence of cervix must be confirmed by clinical records or examination • If indications for hysterectomy unclear, screening may be performed at clinician's discretion	
Follow up in women with CIN in hysterectomy HPE report	Need to be screened with HPV at 6 months and 18 months	
Screening of immunocompromised women	• Start within one year of initiation of sexual activity • HPV testing / Co-testing / Cytology / VIA • Every 2-3 years	• VIA / (Affordable HPV testing if available) • Every 3 years (at least twice as often as general population)

The Bethesda System for Reporting Cytology

Epithelial cell abnormalities

ABBREVIATION	TERMINOLOGY
NILM	Negative for Intra-epithelial Lesion or Malignancy
ASCUS	Atypical Squamous Cells of Undetermined Significance
ASC-H	Atypical Squamous Cells: cannot exclude High grade Squamous Intra-epithelial Lesion
LSIL	Low-grade Squamous Intra-epithelial Lesion
HSIL	High grade Squamous Intra-epithelial Lesion
SCC	Squamous Cell Carcinoma

Glandular cell abnormalities

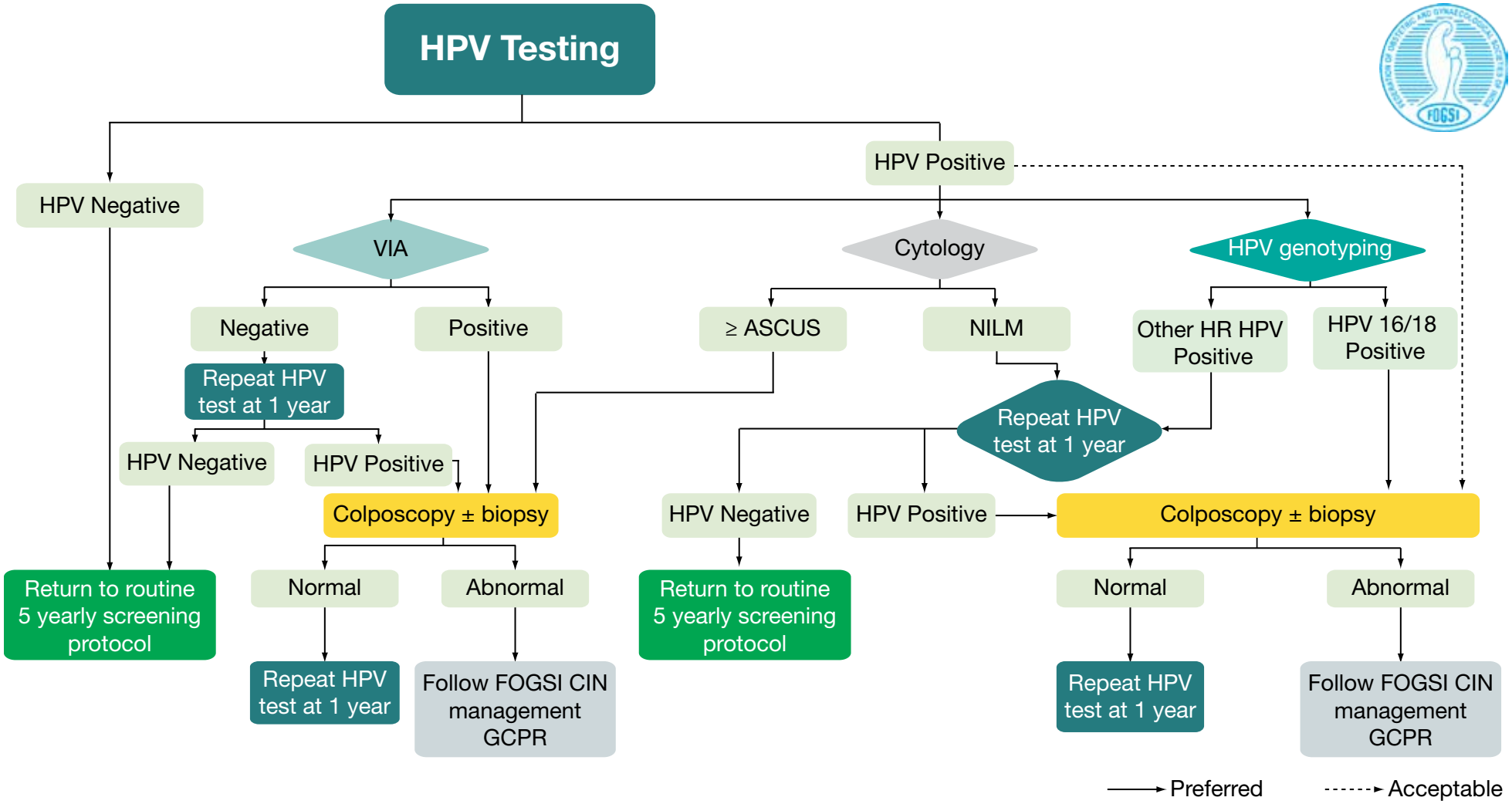
ABBREVIATION	TERMINOLOGY
AGC	Atypical Glandular Cells (specify endocervical, endometrial or NOS, i.e., Not Otherwise Significant)
AGC-FN	Atypical Glandular Cells – Favor Neoplastic
AIS	Endocervical Adenocarcinoma in Situ
Endometrial cells in a woman > 40 years of age	
Adenocarcinoma	
Others	

List of other abbreviations

CIN : Cervical Intraepithelial Neoplasia
ECC : Endocervical Curettage
HPV : Human Papillomavirus
LEEP : Loop Electrosurgical Excision Procedure
TZ : Transformation Zone
VIA : Visual Inspection with Acetic Acid

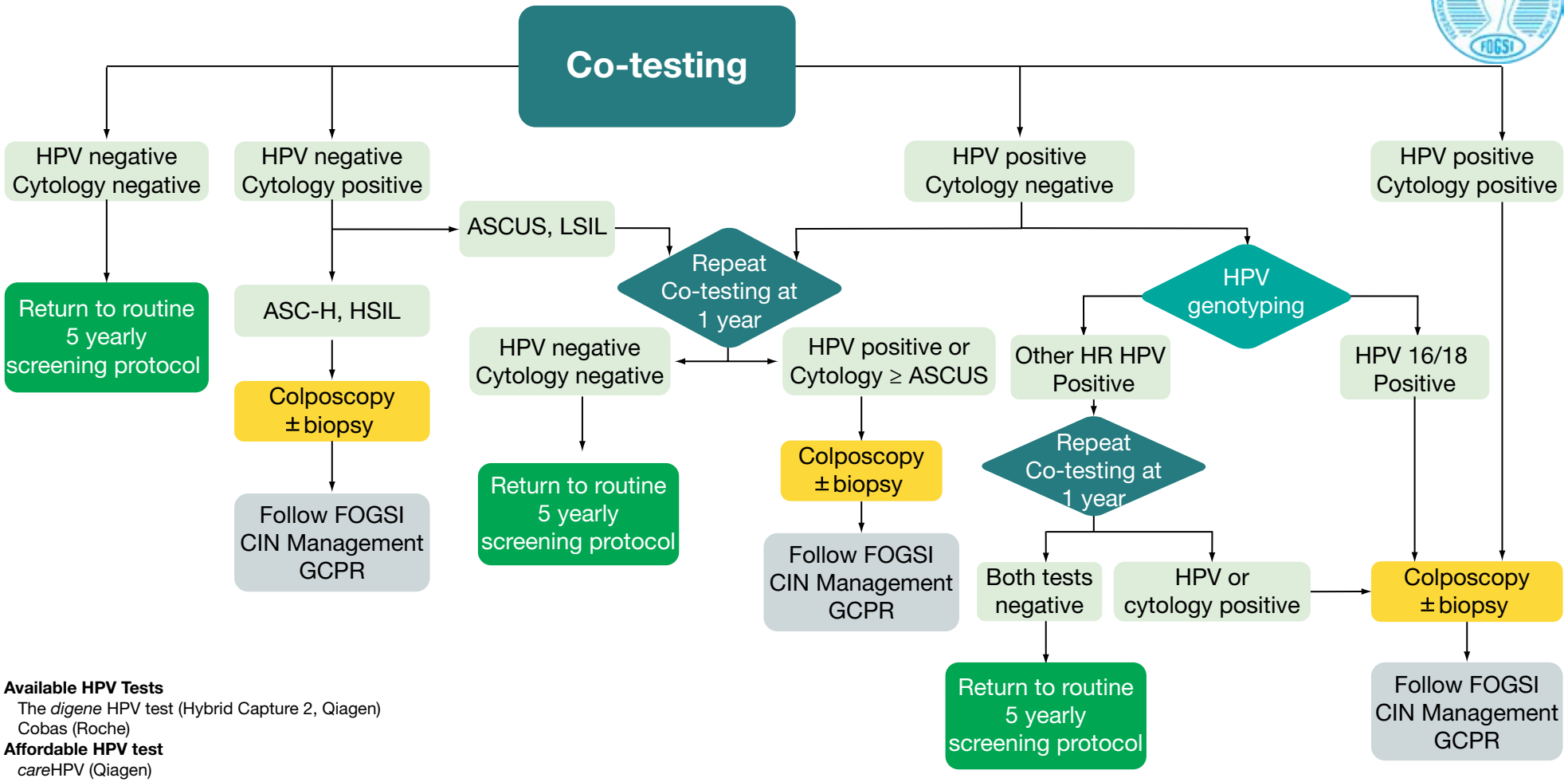
Chart 1

Screening with Primary HPV Testing in women aged > 30 years



Screening with Co-testing (HPV Test with Cytology) in women aged > 30 years

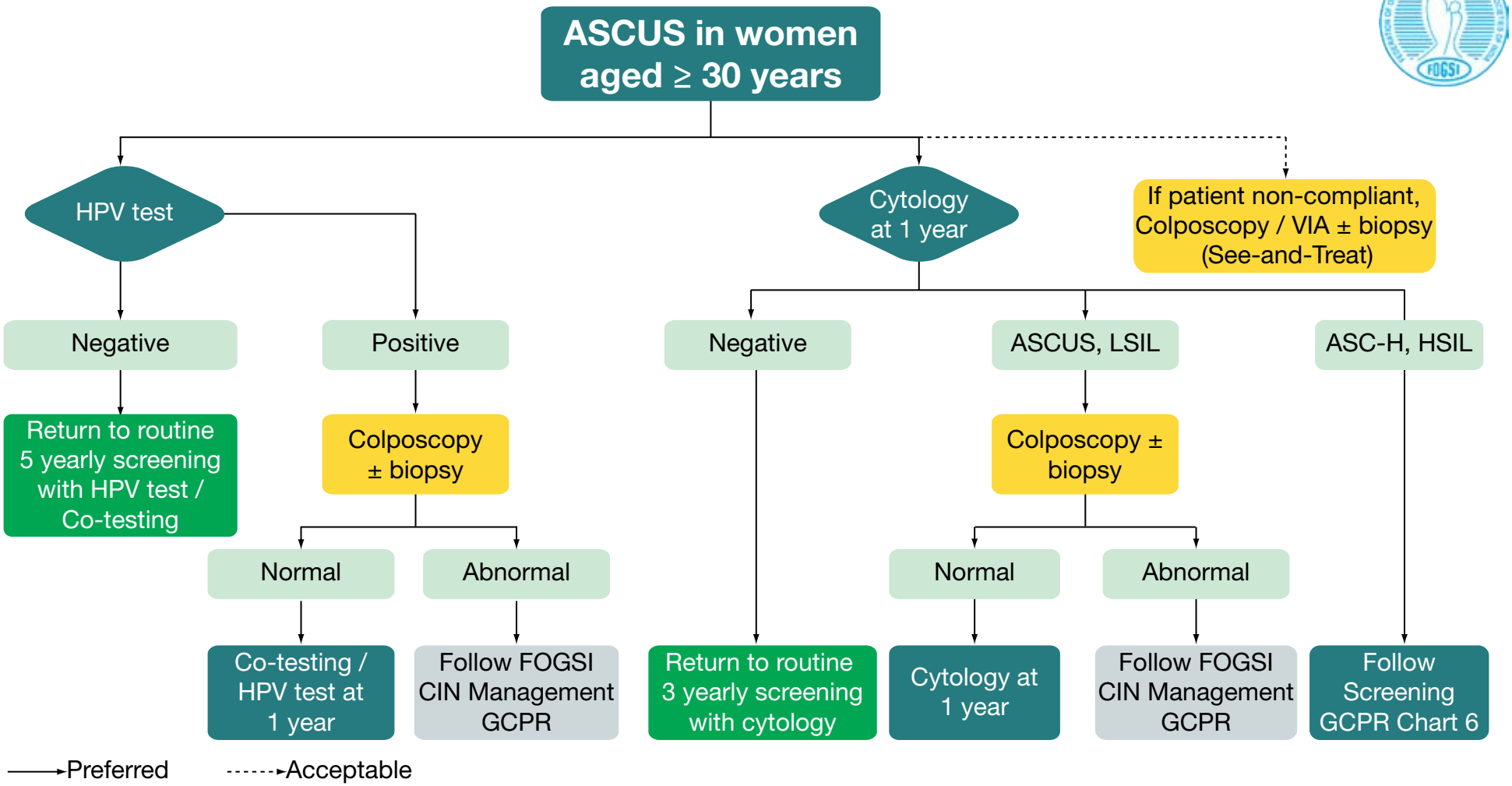
Chart 2



Available HPV Tests
The *digene* HPV test (Hybrid Capture 2, Qiagen)
Cobas (Roche)
Affordable HPV test
*care*HPV (Qiagen)

Chart 3

Screening with Cytology
Management of ASCUS in women aged ≥ 30 years



Screening with **Cytology**
Management of **LSIL** in women aged ≥ 30 years

Chart 4

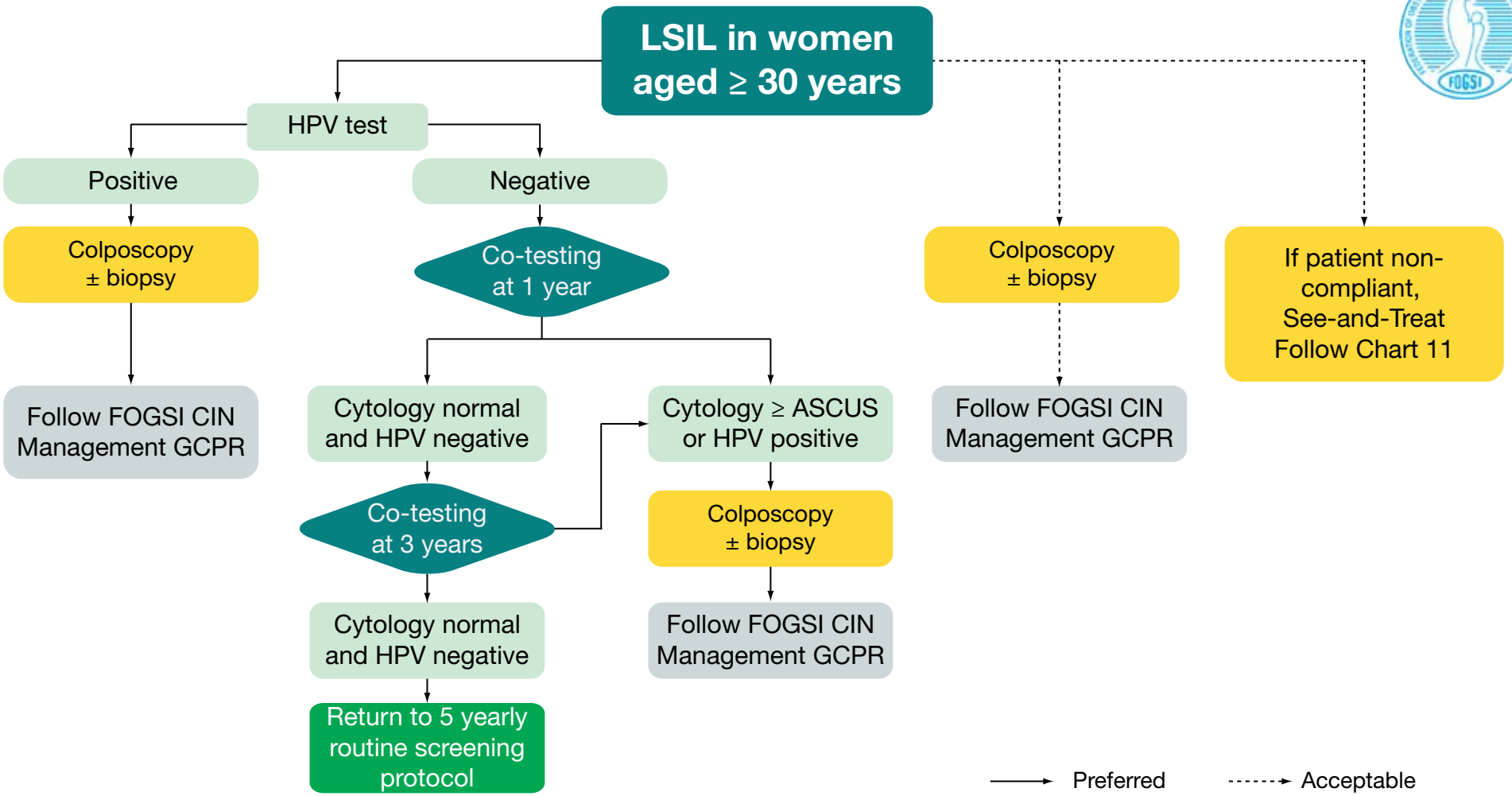


Chart 5

Screening with Cytology
Management of ASCUS / LSIL in women aged < 30 years

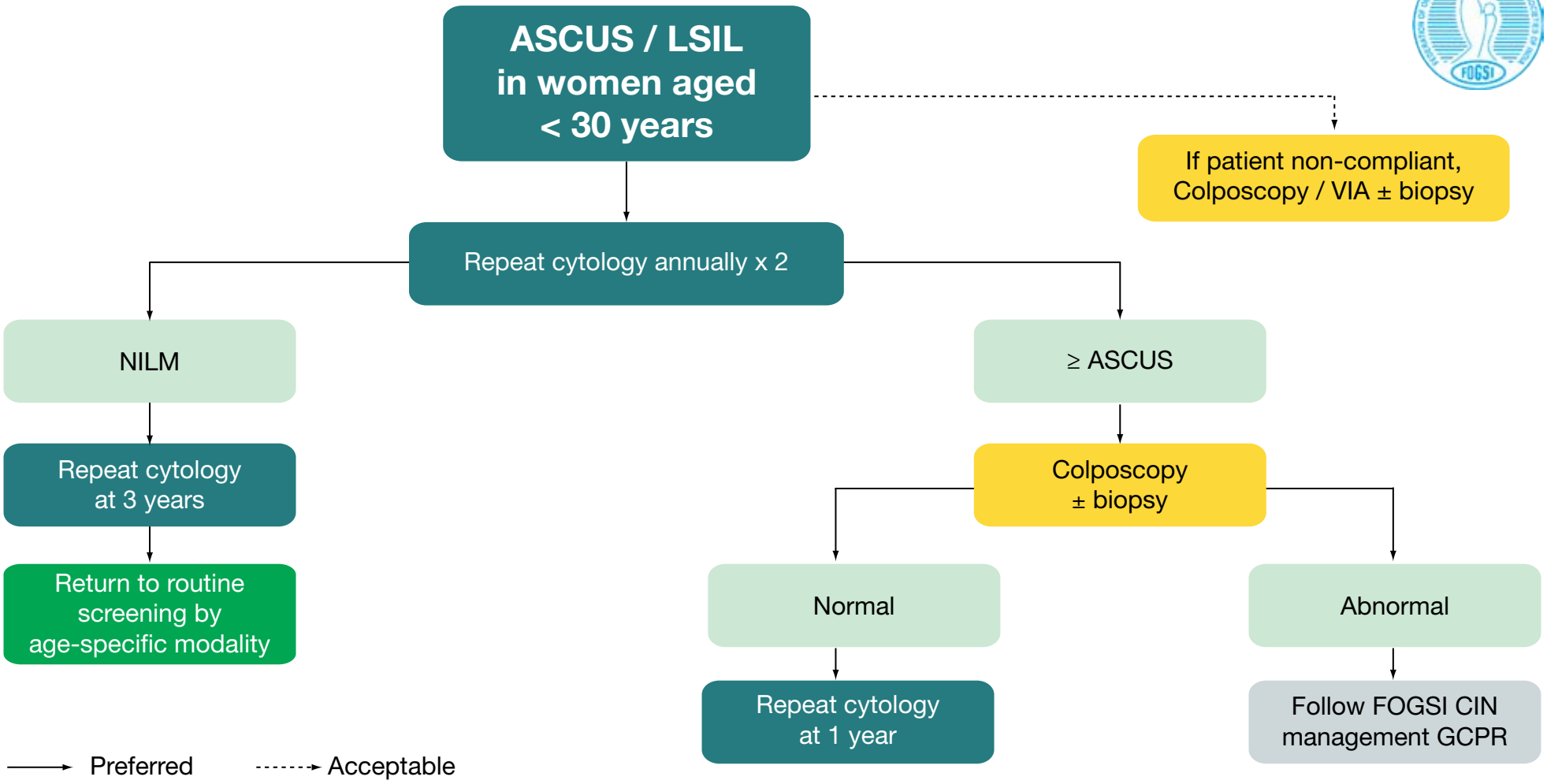
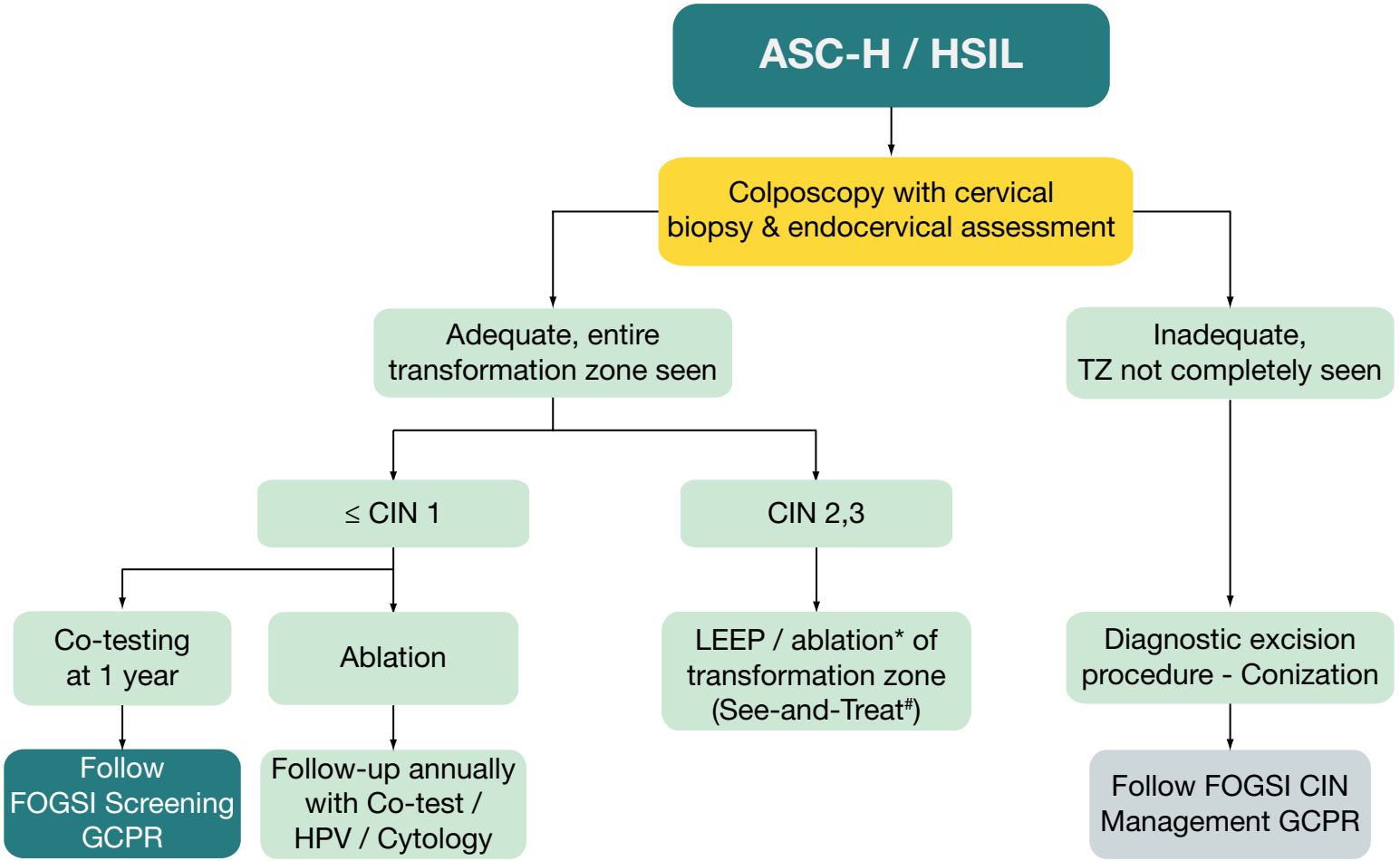


Chart 6

Screening with Cytology
Management of ASC-H / HSIL in women aged > 30 years



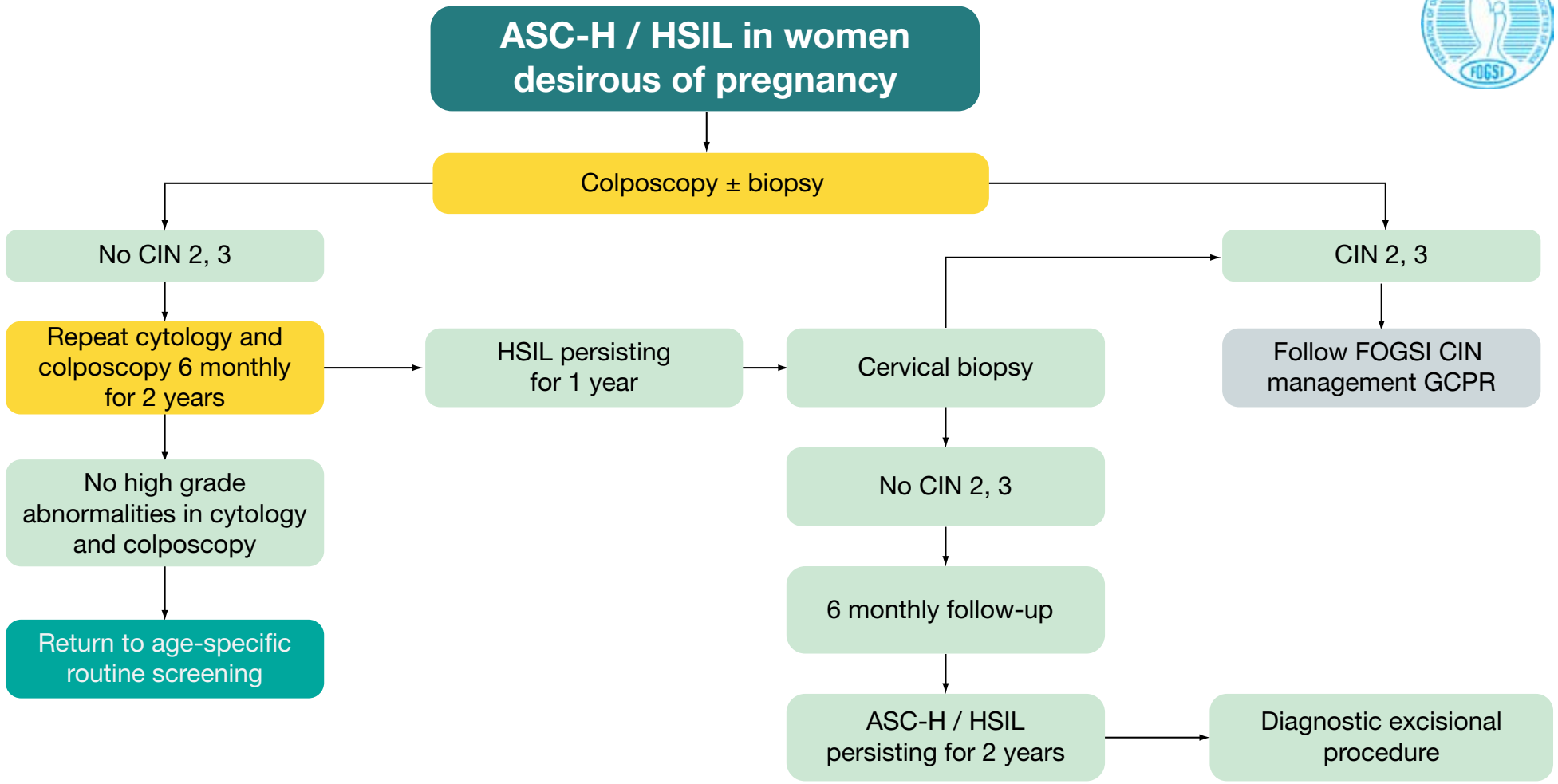
 # Eligibility for See-and-Treat Excision Procedures

1. Lesion should be entirely visible limited to cervix
2. Entire lesion should be located on ectocervix without any vaginal and/or endocervical extension
3. There is no suspicion of invasive cancer
4. Not pregnant
5. See Chart 11 for criteria for ablation

* Ablation can be considered in selected small lesions of CIN 2+

Chart 7

Screening with Cytology
Management of ASC-H / HSIL in women aged < 30 years and desirous of pregnancy



Screening with Cytology
Management of Abnormal Glandular Cells:
Atypical Endometrial Cells

Chart 8

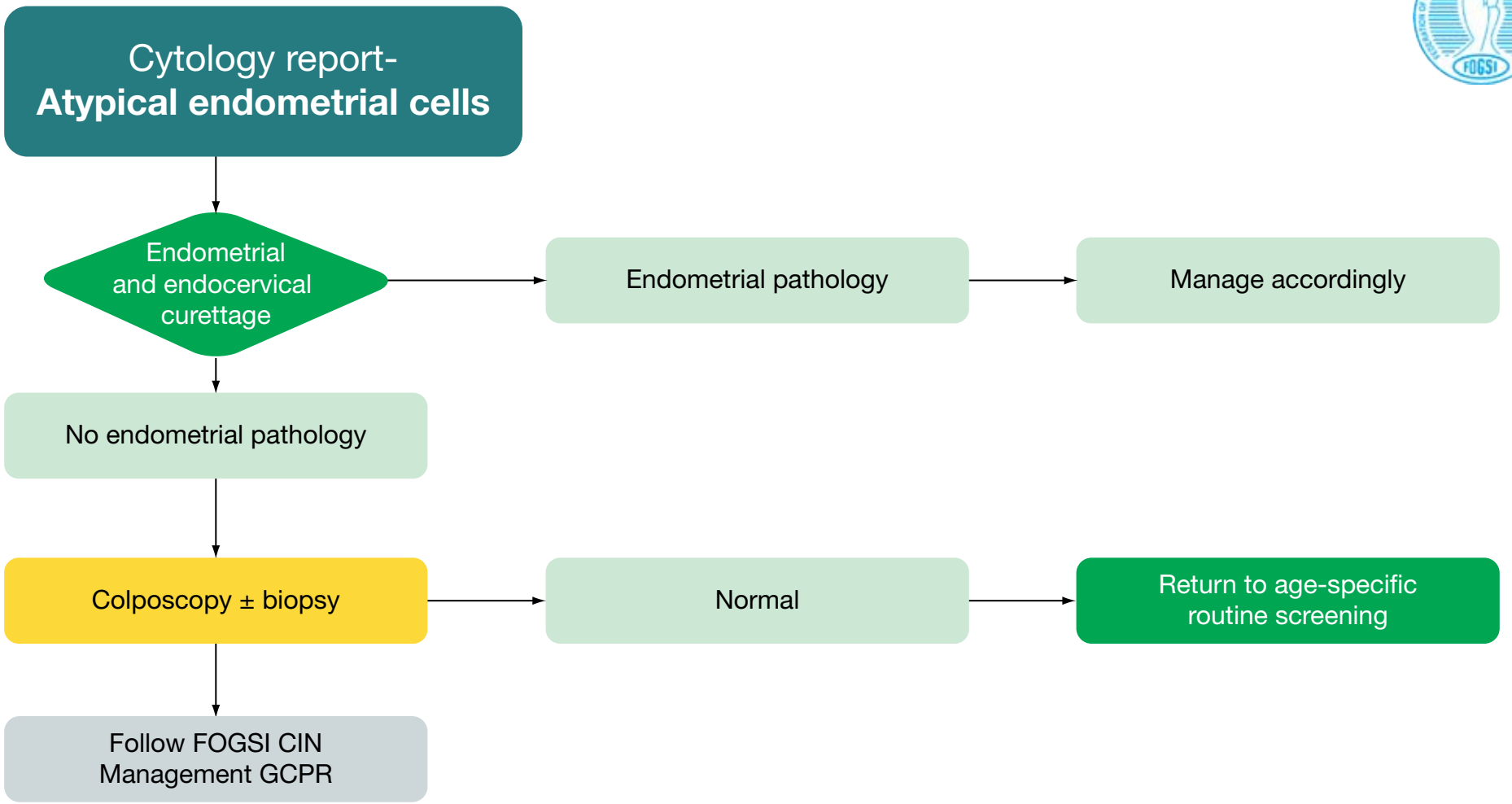
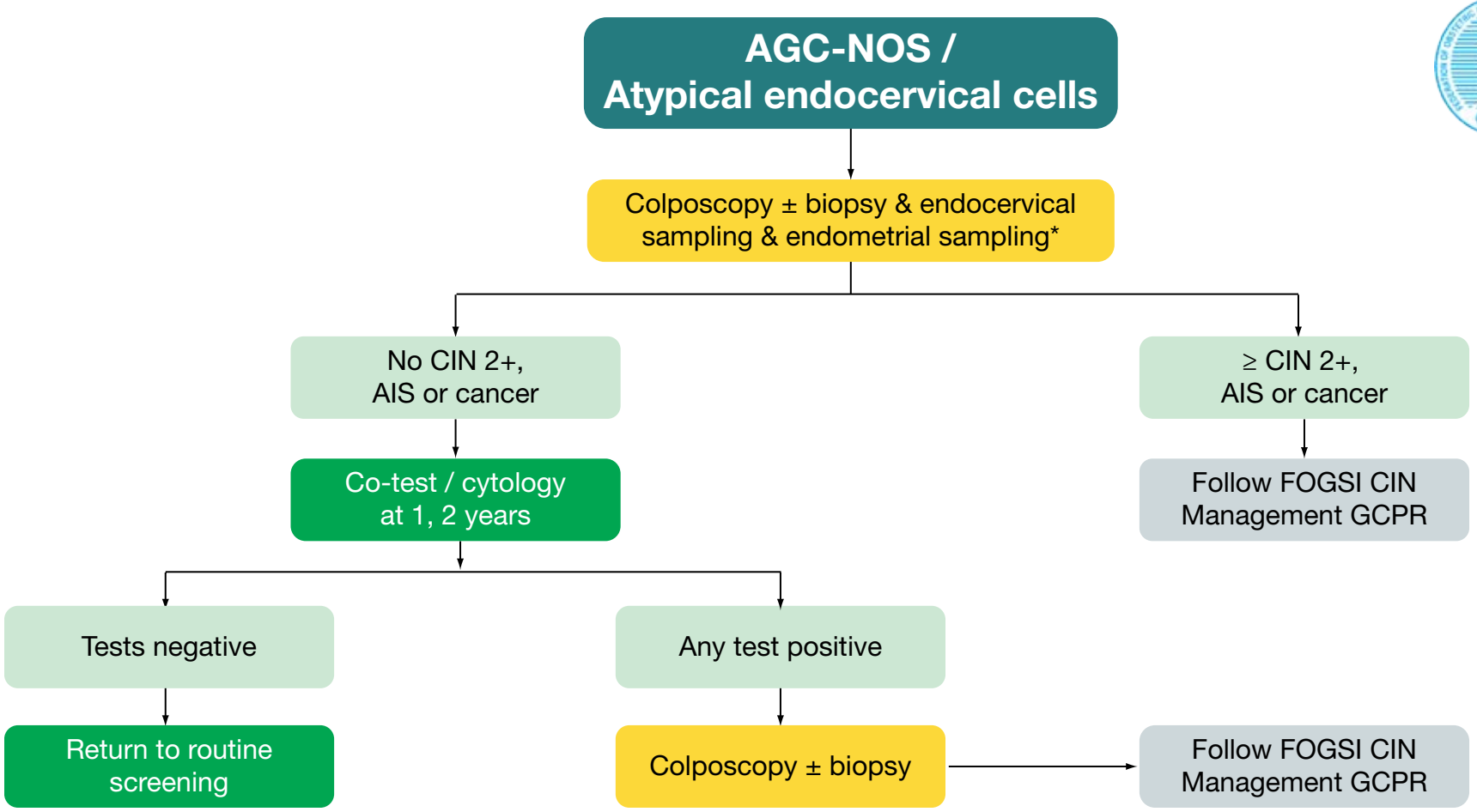


Chart 9

Screening with Cytology
Management of Abnormal Glandular Cells:
AGC-NOS / Atypical Endocervical Cells

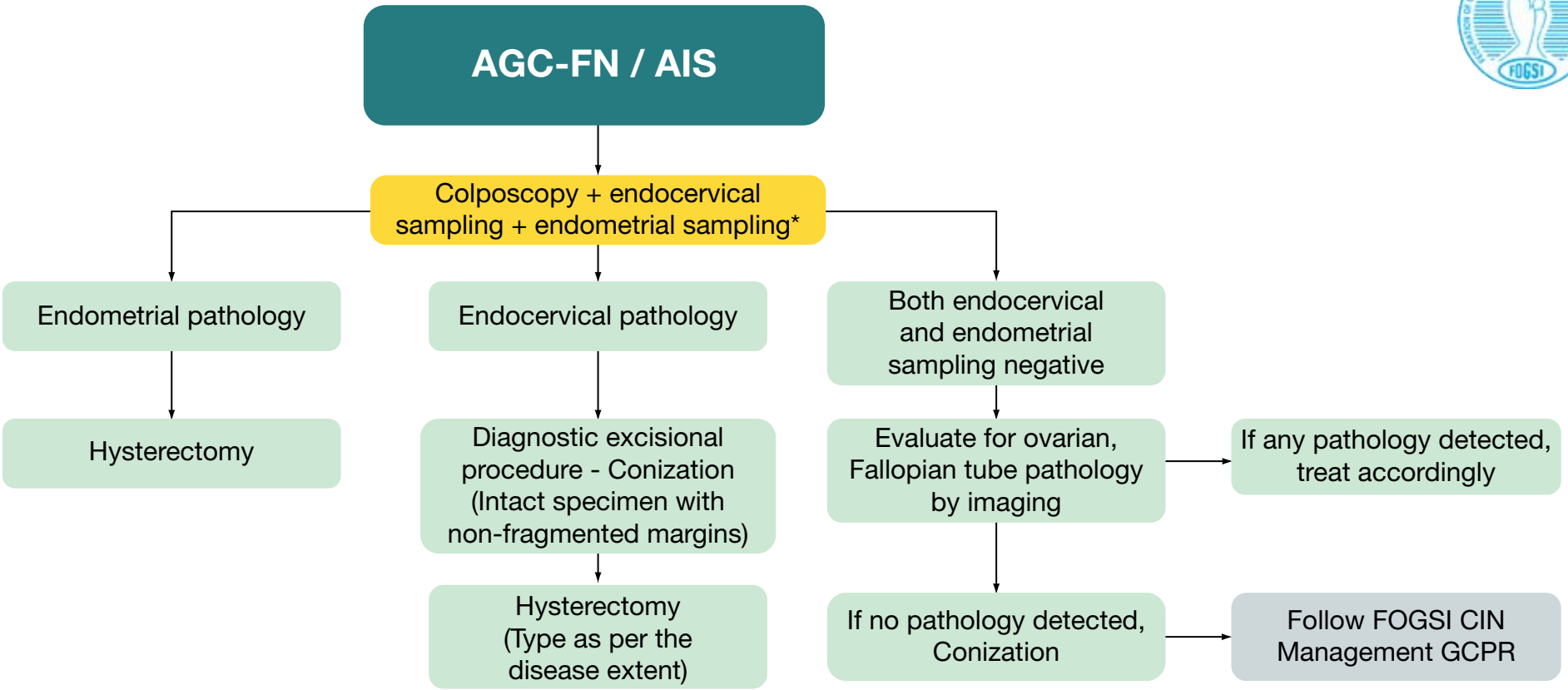


*Age > 35 yrs, high risk factors, e.g., obesity, chronic anovulation

AGC - NOS: Atypical Glandular Cells - Not Otherwise Specified; AIS - Adenocarcinoma in Situ

Chart 10

Screening with Cytology
Management of Abnormal Glandular Cells: AGC-FN / AIS

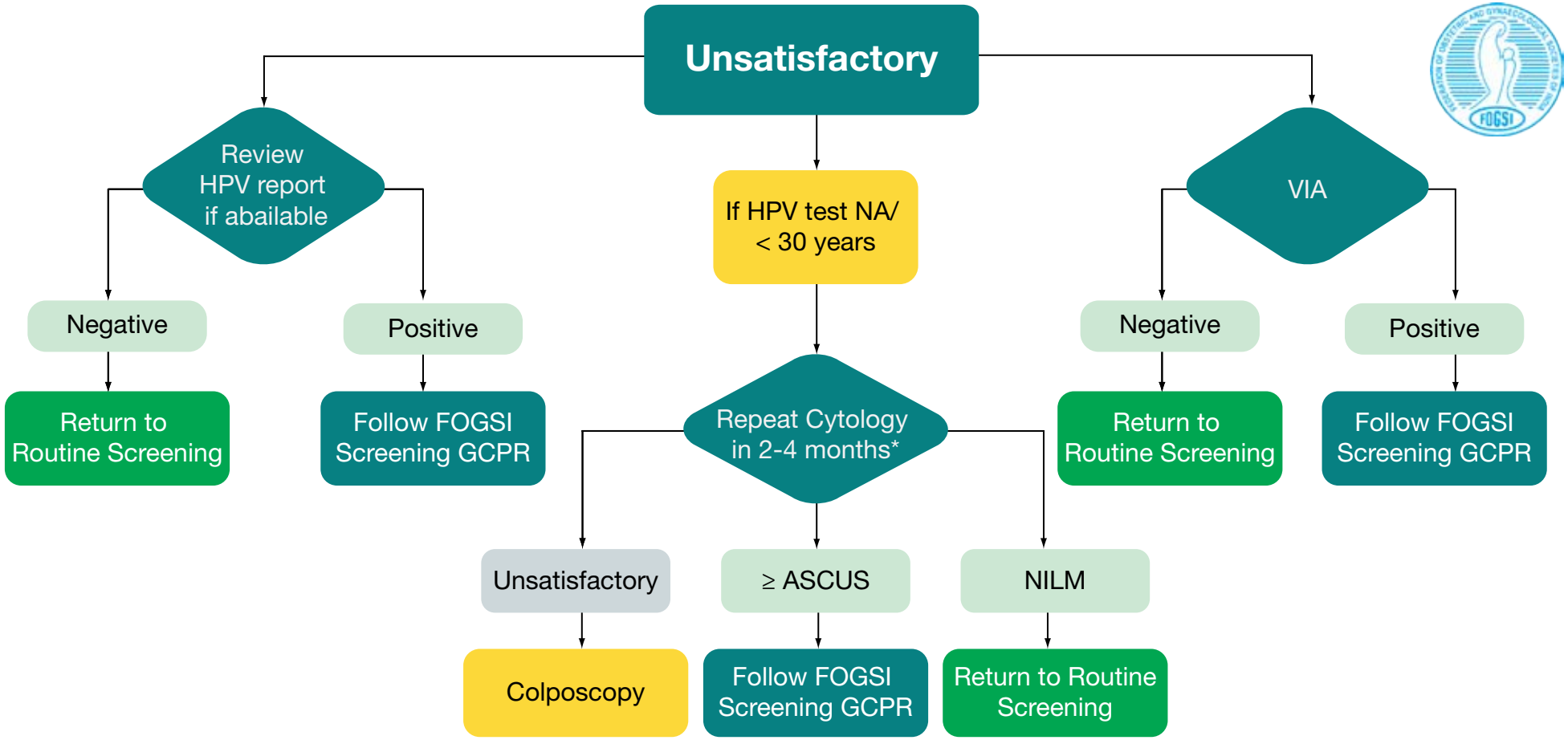


*Age > 35 yrs, high risk factors, e.g., obesity, chronic anovulation

AGC-FN - Atypical Glandular Cells Favouring Neoplasia; AIS - Adenocarcinoma in Situ

Chart 11

Unsatisfactory Smear



*consider LBC if facilities available
*In postmenopausal female local estrogen x 3 weeks, and stop 1 week prior to testing

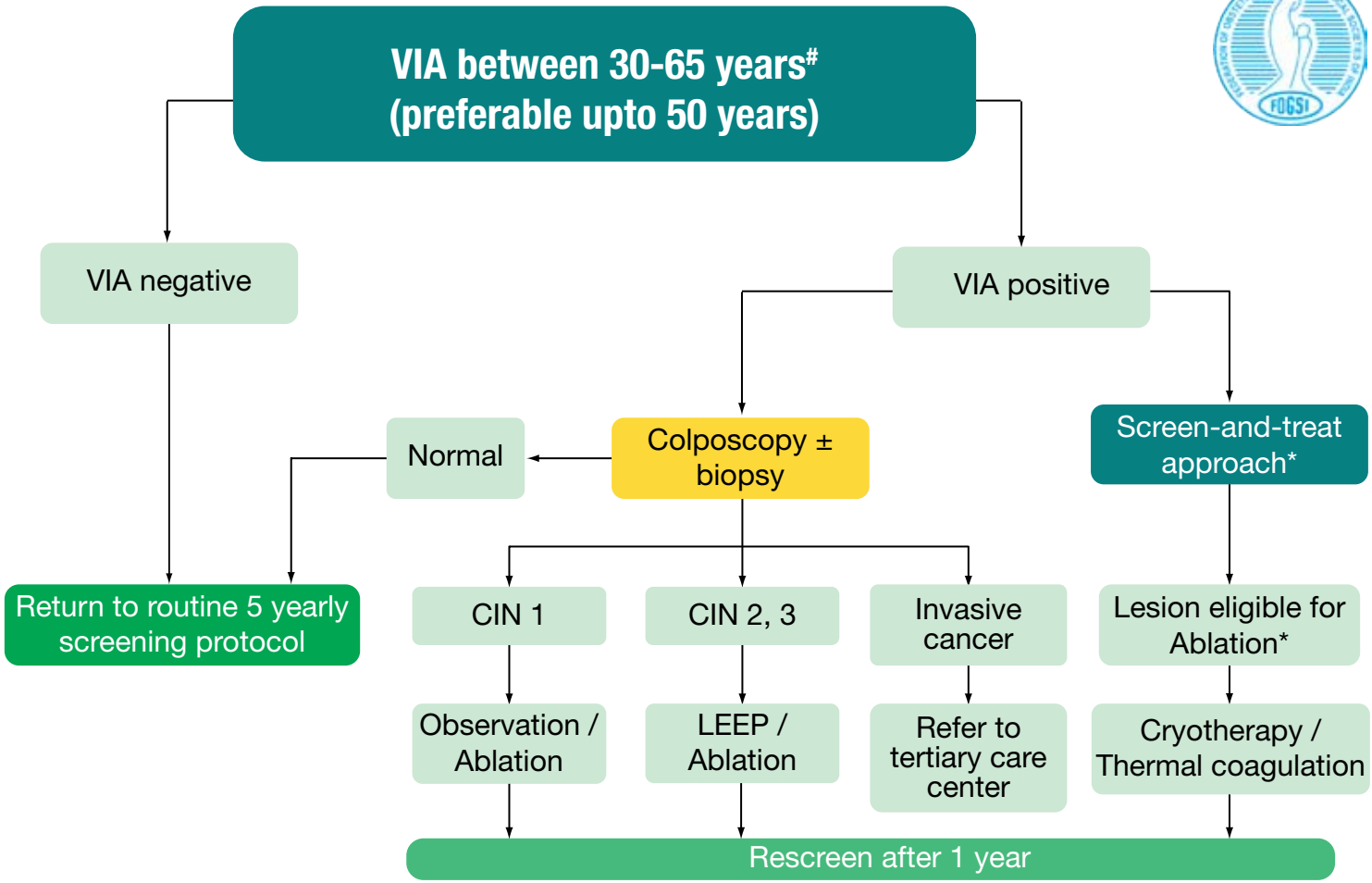
Chart 12

Screening with **VIA** in women aged 30-65 years

*** Eligibility for Screen-and-treat (Ablative Procedures)**

1. Lesion should be entirely visible and occupy not more than two quadrants of cervix
2. Entire lesion should be located on ectocervix without any vaginal and/or endocervical extension
3. Lesion can be adequately covered by largest cryotherapy probe available (Multiple overlapping applications with thermocoagulation)
4. There is no suspicion of invasive cancer
5. Screen-and-treat by cryotherapy is contraindicated in cases of postcoital or postmenopausal bleeding, obvious cervical growth, irregular surface or bleeds on touch

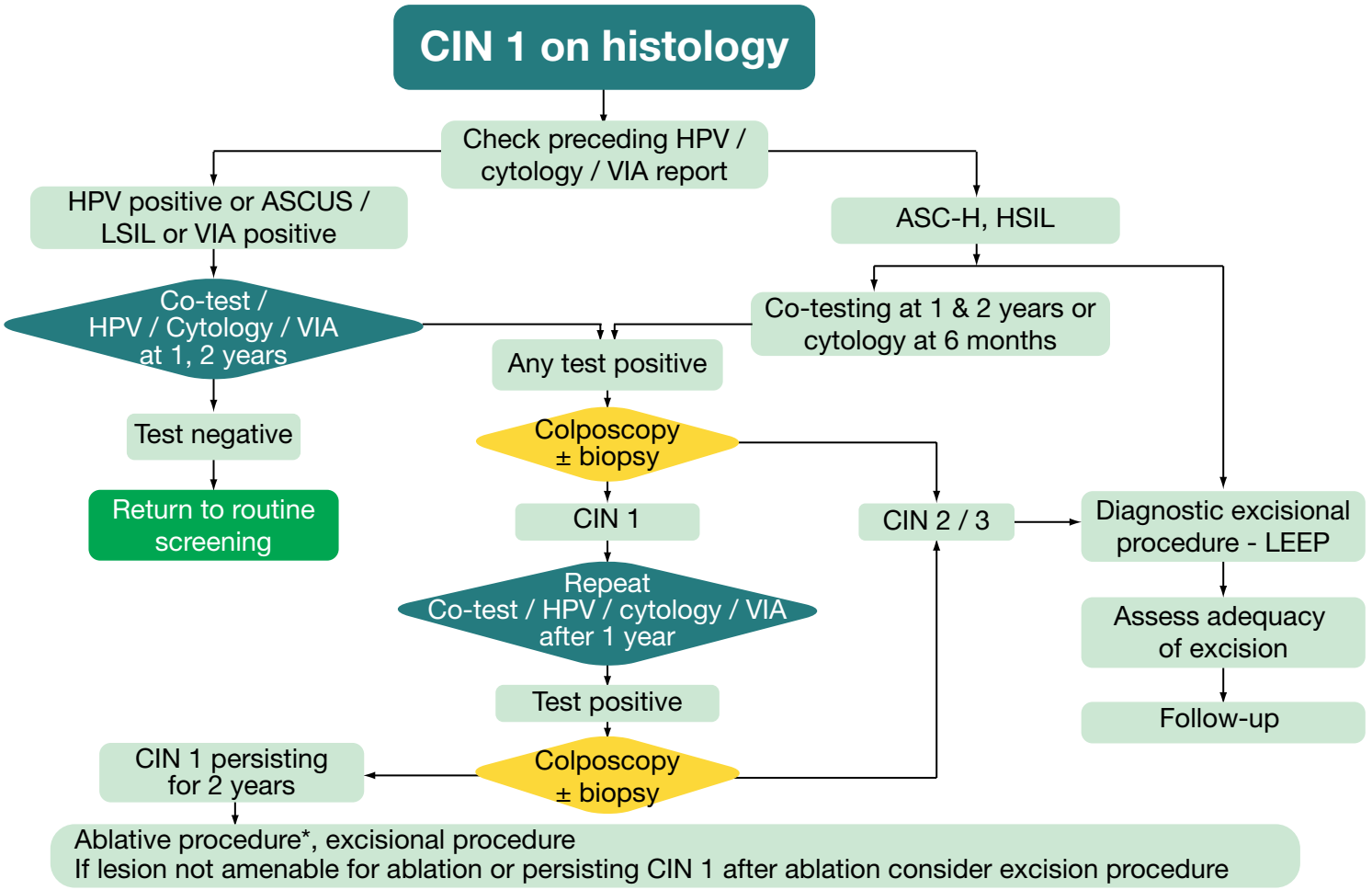
N.B. Biopsy can be taken prior to ablation, if feasible, for post-hoc correlation



Recommendation of Ministry of Health & Family Welfare, Government of India

Chart 13

Management of Women with CIN 1 on Histology



*** Eligibility for Ablative Procedures**

1. Lesion should be entirely visible and occupy not more than two quadrants of cervix
2. Entire lesion should be located on ectocervix without any vaginal and/or endocervical extension
3. Lesion can be adequately covered by largest cryotherapy probe available
4. There is no suspicion of invasive cancer

Chart 14

Management of Women Desirous of Pregnancy with CIN 1 on Histology

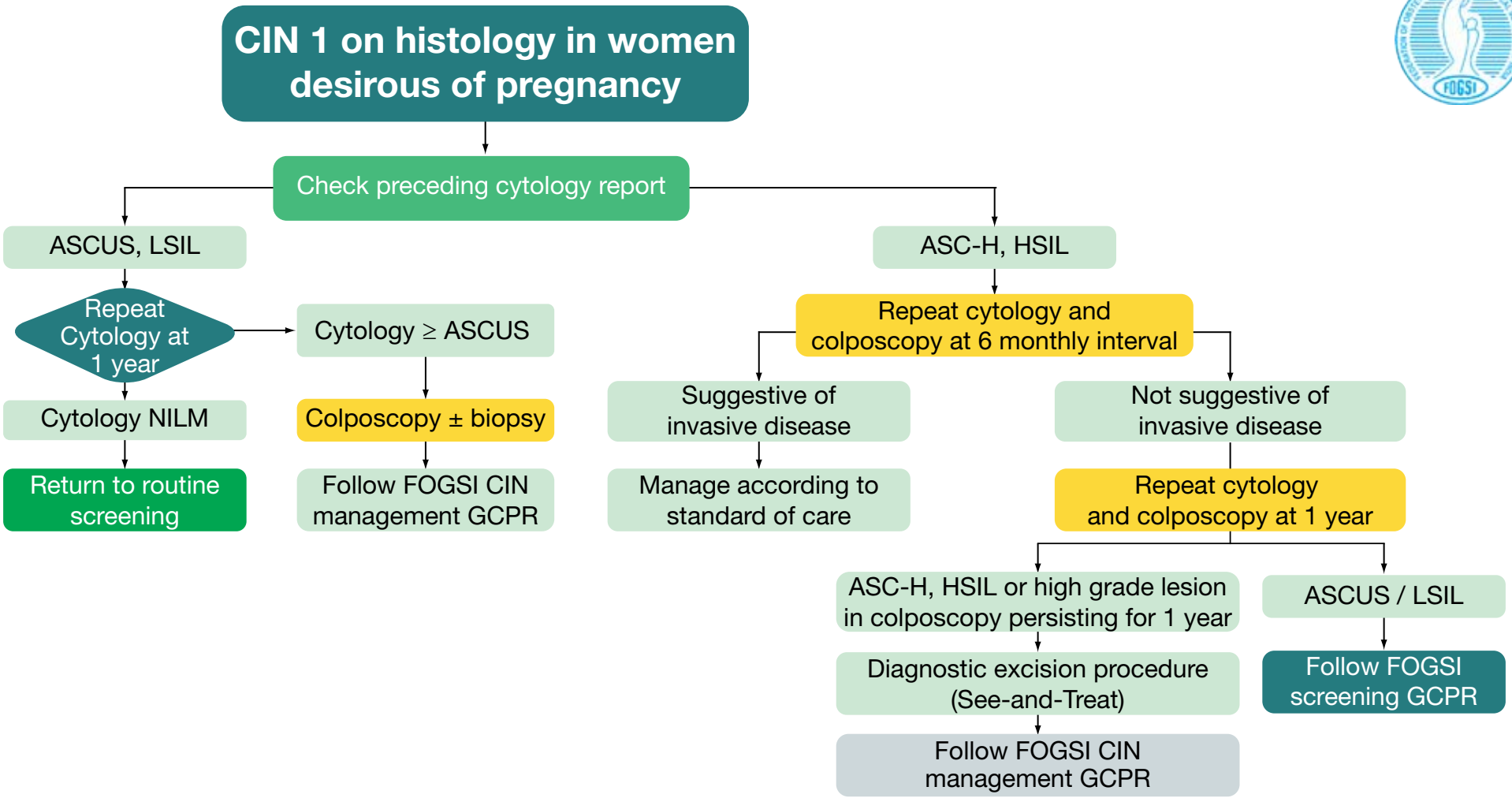
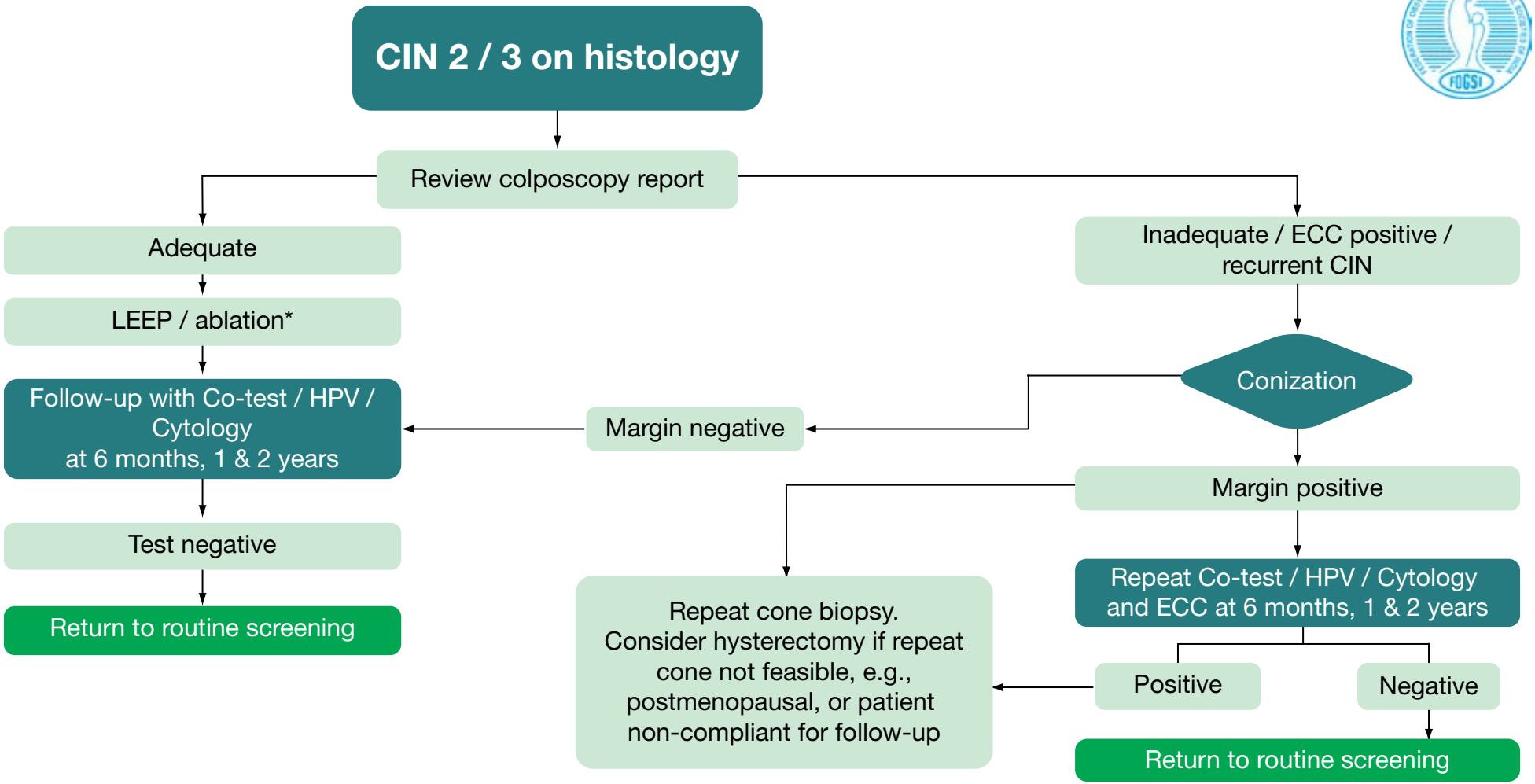


Chart 15

Management of Women with CIN 2, 3 on Histology



Management of Women with CIN 2, 3 on Histology, Desirous of Pregnancy

Chart 16

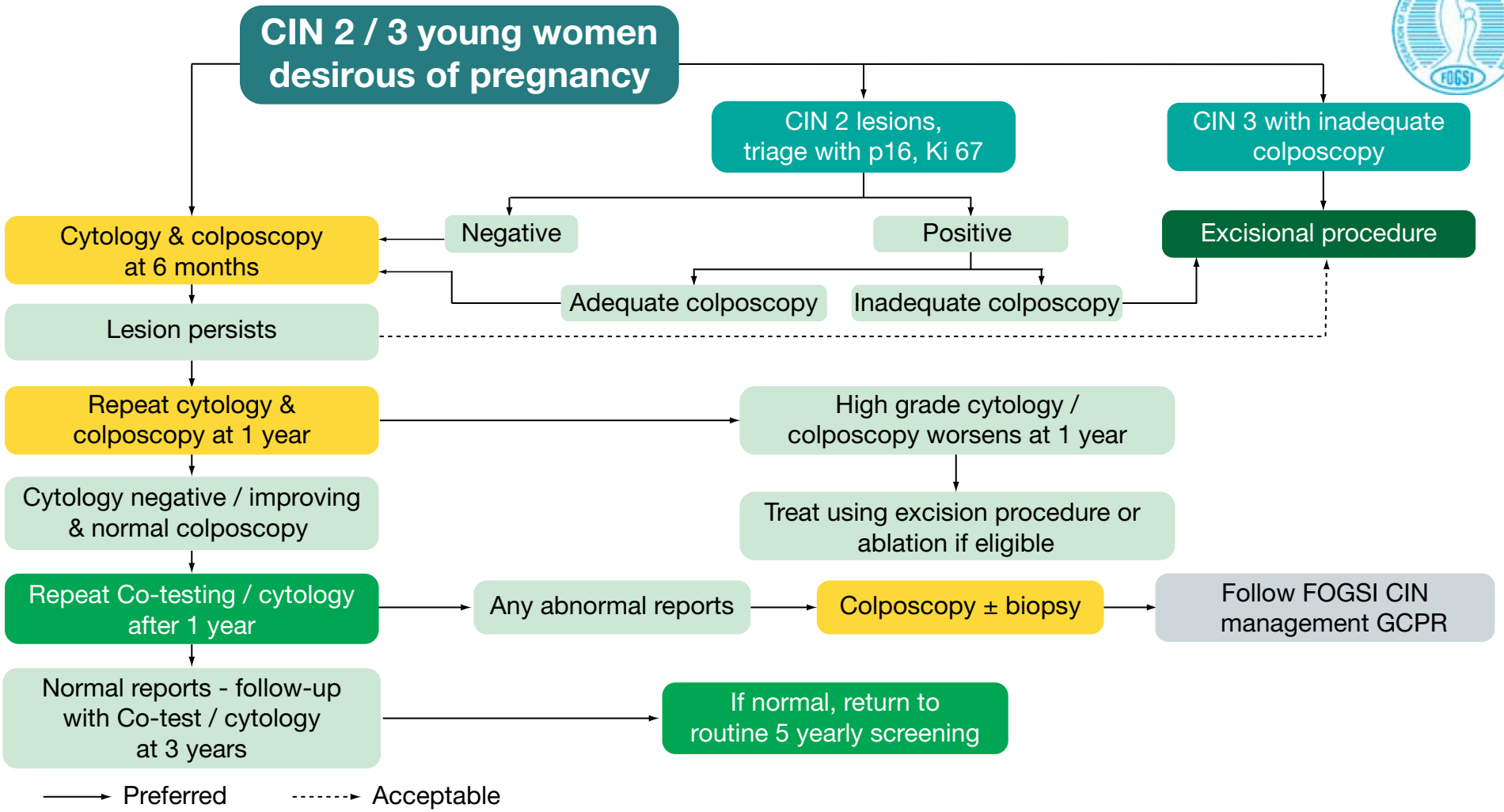
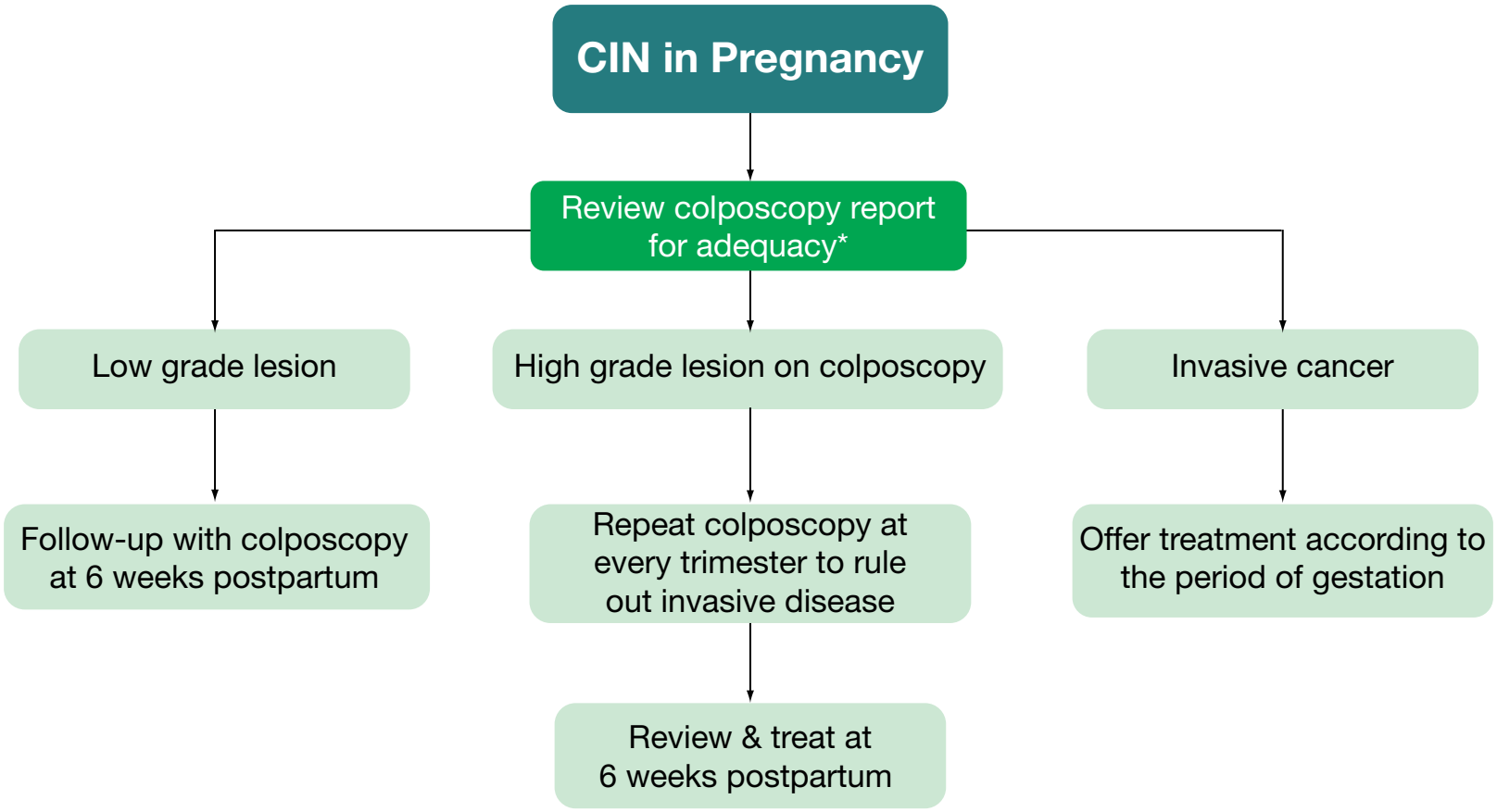


Chart 17

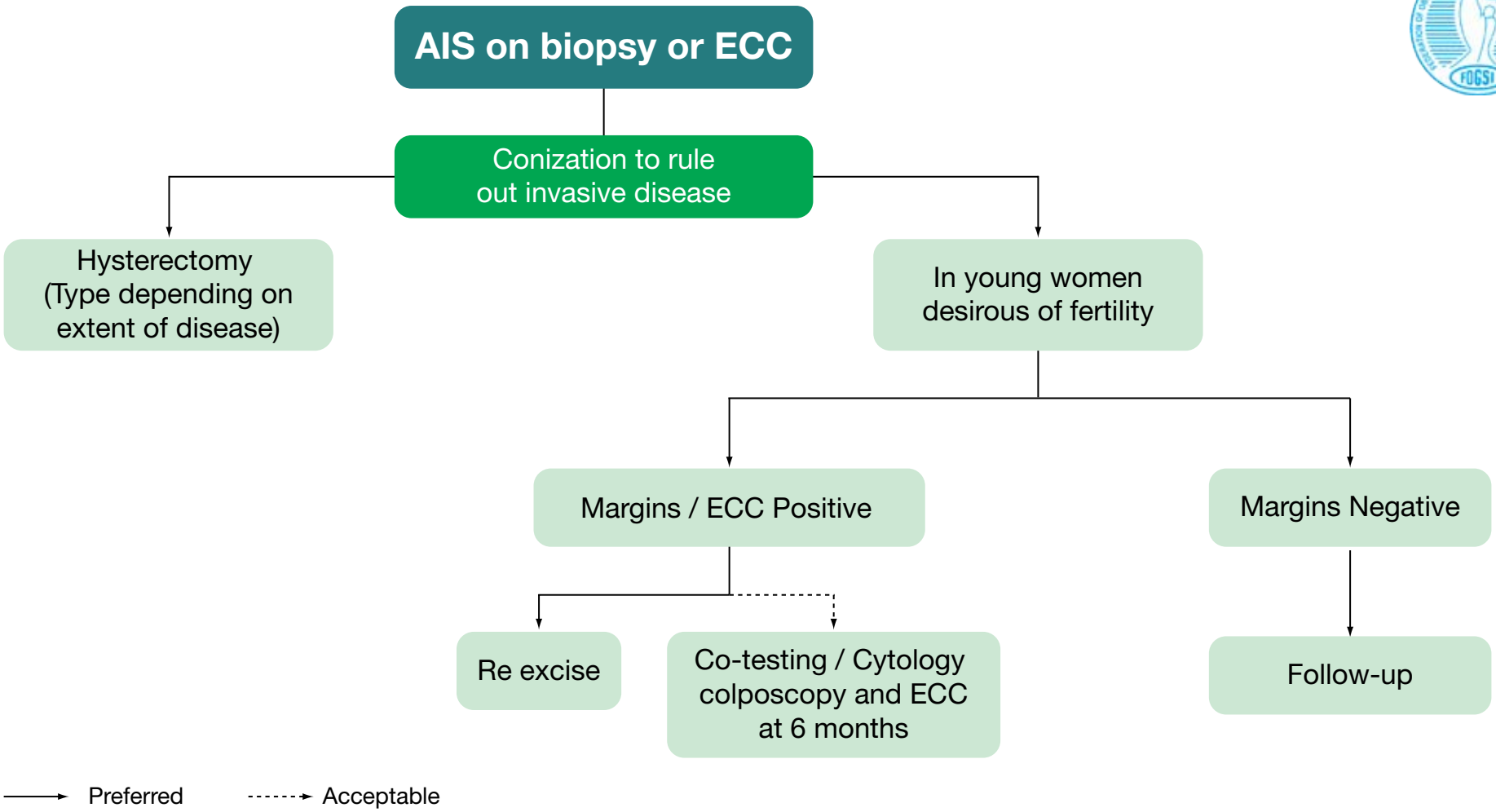
Management of Women with CIN in Pregnancy



* ECC should be avoided in pregnant women

Chart 18

Management of Women with AIS



Newer modalities: Cytology-based screening

	LIQUID-BASED CYTOLOGY (LBC)	BIOMARKERS
Options	ThinPrep (Hologic), SurePath (BD)	p16INK4a : CINtec (Roche), CINtec PLUS (p16INK4a + Ki-67)
Advantage	Few inadequate Pap samples (1.9%) Reflex HPV testing possible Automated reading possible	Identify transforming HPV infection Detect CIN 2 + disease Triage low-grade smears Can be done with histology and cytology slides Reduce colposcopy referrals
Efficacy	Sensitivity not better than conventional (RR 1.1); 11% more sensitivity for LSIL + lesions	Sensitivity:64-92%, Specificity: 41-96% for low-grade smears
Limitations	More expensive, not cost-effective Automated not effective	Wide variation in reported sensitivity, lack of standardized reporting Need for substantial expertise False positive rates high

Newer modalities: HPV-based screening

	VAGINAL SELF - COLLECTION	E6 E7 MRNA	DNA METHYLATION (DNAME)	MARKERS OF ABERRANT S-PHASE INDUCTION
Options	Delphi device, Evalyn sampler	APTIMA, APTIMA HPV GT (Hologic) Oncotect (Incell Dx)	QIAsure Methylation Test (Qiagen)	Topoisomerase IIA (TOP2A) and MCM2 (BD)
Advantage	Acceptable, eliminates cost of visiting a clinician	Effective triage for low-grade smears Reduce colposcopy referral by 68% compared to 30% by HPV DNA testing	Alternative triage for hrHPV Automated, objective test Run on the same sample as the HPV assay	Identify transforming HPV infection
Efficacy	Sensitivity variable: 60-90% Overall 3.4 (95% CI=2.4-4.9) times more CIN 2+ detected by self-collected HPV samples than by routine cytology.	Sensitivity: 90-95%, Specificity: 42-61%, PPV: 67%	CADM1-m18 combined with MAL-m1 methylation: Sensitivity: 60.5%- 100%, Specificity: 22.7% to 83.3% (95% CI: 78.4-87.4).	Sensitivity: 67-99% , Specificity: 61- 85%.
Limitations	Inadequate sample possible, Woman- dependent, reluctance to use medical devices	Expensive	Expensive, wide variation in reported sensitivity	Research settings

ABOUT PSI

PSI India is a non-profit, non-governmental organisation enabling people of India to lead healthier lives and plan the families they desire by marketing affordable products and services. We assist and complement the efforts of the Government of India (GoI) in the priority areas – Family Planning, Non Communicable Diseases including Cervical Cancer Prevention, Maternal and Child Health, Sanitation and Gender-based Violence. We use social marketing models and enable quality products and services to reach people at a price they can afford. We apply commercial strategies to the non-profit health sector, allowing women to access care in a place that is convenient, and in a way, they can understand. We are one of the largest organisations in India with many human assets working in several States and Union Territories across India. We believe in creating healthy communities and working conditions.

Management and Coordination: Ms. Deepti Mathur, *Senior Specialist, Knowledge Management, PSI*
Dr. Parul Saxena, *Assistant Manager, PSI*

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